REMARKS

The Official Action of June 3, 2003 has been carefully considered and reconsideration of the application as amended is respectfully requested.

The specification has been amended to make changes of an editorial and clerical nature. The informality noted by the Examiner at paragraph 2 of the Official Action has been addressed and corrected.

The requirement for correction of the drawings has been noted and proposed replacement drawings are submitted herewith.

The claims have been amended in accordance with the disclosure in the specification as filed at, for example, the paragraph bridging pages 18-19 of the specification, which describes how the levels of expression of IFN alpha 5 mRNA are significantly reduced in the liver tissue of patients with chronic hepatitis C in comparison with that expressed in the livers of healthy patients. As discussed in the specification at page 18, line 27 to page 19, line 2, mRNA values for IFN alpha 5 in normal livers range 0.43 ± 0.12 versus 0.12 ± 0.03 in livers of patients with chronic C hepatitis -HCV- (75% lower than in controls consequently). The specification as filed also provides support for "cirrhosis caused by hepatitis C virus" (see, e.g., specification at page 3, lines 1-4, and page 8, lines 12-16).

The above amendment to the claims removes the basis for the rejection under 35 USC 112, second paragraph, appearing at paragraph 4b of the Official Action.

Applicants respectfully traverse the rejection at paragraph 4a of the Official Action on the grounds that IFN alpha 5 is not an arbitrary name, but is in fact a designation that is well understood by those of skill in the art as identifying a

particular subtype (chemical species) of IFN-alpha. This is shown, by way of example, by the Foster et al article cited by the Examiner at paragraphs 6-7 of the Official Action. The article clearly shows that "IFN-alpha 5" is distinguishable from other subtypes of IFN-alpha and has a recognized meaning to those of skill in the art. Accordingly, it is respectfully submitted that all claims presently of record are sufficiently definite to satisfy the dictates of 35 USC 112, second paragraph.

The Examiner has rejected claims 11, 21, 22 and 23 under 35 USC 112, first paragraph, for alleged lack of enablement. Applicants respectfully traverse this rejection.

Applicants first note that the specification as filed states unequivocally that, when a patient is infected by HCV, there is a marked reduction in the expression of IFN-alpha 5 in the liver of the patient (see specification in the paragraph bridging pages 18 and 19, and on page 19 at lines 6-8), and that the claims as amended are directed to a method that recites the step of administering IFN-alpha 5 to the patient to raise the level of IFN-alpha 5 in the patient (rather than "to treat the disease"). As discussed in MPEP Section 2164.04, where as here a specification disclosure contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, the specification disclosure must be take as being in compliance with the enablement requirement of 35 USC 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained in the specification.

In the present case, it is respectfully submitted that the Examiner has not presented sufficient reasoning to cast doubt on the accuracy of Applicants'

presumptively accurate disclosure. The experimental results described in the paragraph bridging pages 18 and 19 of the specification, and summarized in Figure 1B, show the reduced levels of expression of IFN-alpha 5 mRNA in patients with chronic hepatitis C. Based on this experimental evidence, the Applicants concluded that, in infection by HCV, there is a marked reduction in the expression of the IFN-alpha subtype normally expressed in liver tissue. There is nothing in the Examiner's comments in the Official Action that is inconsistent with such conclusion. Indeed, the bulk of the Examiner's comments pertain to issues that are no longer relevant due to the amendment of the claims. In particular, the claims no longer recite "lower than normal" and "to treat the disease", and there is no reason why Applicants would need to show effectiveness in treating a disease to support their presumptively accurate disclosure.

Even assuming for the sake of argument that the Examiner had cast sufficient doubt on the accuracy of Applicants' presumptively accurate disclosure to shift the burden to Applicants of presenting evidence to support their position, it is respectfully submitted that they could meet this burden. There is a strong presumption that if normal levels of IFN alpha 5 are depleted in liver diseases, as in HCV, that natural occurring polypeptide of liver origin may play a role in defending the liver from the viral infection. That nexus is clearly indicated throughout the specification. Moreover, in a paper sent recently for publication (not yet published) by some of the inventors of the present US application, the specific antiviral action in liver of IFN alpha 5 is compared with other well known interferon subtype (IFN alpha 2) broadly used in antiviral therapy of HCV. The paper (submitted herewith with a Declaration

Under 37 CFR 1.132) shows that the antiviral action attributed to IFN alpha 5, measured as cell signaling and antiviral genes induction, was more efficient and intense than when IFN alpha 2, was used. Although only HCV therapy is exemplified, the role of liver defense of IFN alpha 5 would not be expected to differ in other liver diseases of viral origin, including in particular cirrhosis caused by hepatitis C virus which is the final pathophysiological step of a chronic hepatitis viral infection.

Claims 11-15, 21 and 23-27 stand rejected under 35 USC 102(b) as allegedly being anticipated by Foster et al. The remaining claims stand rejected under 35 USC 103(a) as allegedly being unpatentable over Foster et al either alone or in view of Wallner et al or in view of Wallner et al and Salmanian et al. Applicants respectfully traverse these rejections.

Applicants first note that Foster et al describe the *in vitro* activity of a number of different IFN-alpha subtypes whereas the claims are all directed to a method for treating a patient by the administration of the recited protein, or nucleotide coding the same, **to the patient**. Under these circumstances, there cannot be any question of an anticipation under the provisions of 35 USC 102. Moreover, as recognized by the Examiner in the first full paragraph on page 5 of the Official Action, those of skill in the art would appreciate that there is often no known correlation between *in vitro* and *in vivo* results. Assuming this to be the case, the Foster et al reference could not be considered to provide even a reasonable expectation of success in using **any** of the IFN-alpha subtypes described therein to treat a patient.

In any event, Foster et al do not show or suggest the use of IFN-alpha 5 to treat a liver disease in a patient marked by insufficient expression of IFN-alpha 5 in the

liver of the patient. Indeed, although the present specification shows that there is a marked reduction in the expression of IFN-alpha 5 in liver tissue of a patient with a viral liver disease selected from the group consisting of chronic hepatitis C, cirrhosis and hepato cellular carcinoma, there is nothing to show or suggest this in the cited art. Foster et al show the anti-viral activity of several subtypes of IFN, including IFN-α5, *in vitro* (in human liver tumor cell lines) against EMC (murine encephalomyelitis) virus. The reference does not show whether or not IFN-α5 has a preference for any particular tissue, and the reference acknowledges that the role of each type I IFN remains obscure (page 1032, right column). Indeed, after presenting an initial hypothesis that the existence of a multiplicity of alpha IFN subtypes might be due to different tissue responses to particular subtypes, the reference leads in the opposite direction by acknowledging that this hypothesis was not supported by the results reported in the reference (page 1032, right column). To the contrary, the results show that the antiviral properties of the different subtypes were broadly similar in the three (3) tissues/cell lines tested (one of which was a liver tumor cell line). Accordingly, the Foster reference does not teach, and in fact teaches away from, an expectation that IFN-α5 might be effective in any particular tissue.

In the absence from the cited references of any showing or suggestion of a reduction in the expression of IFN-alpha 5 in liver tissue of a patient having any of the recited viral liver diseases, there would be nothing to provide either a motivation for the administration of IFN-alpha 5 to the patient or an expectation that such administration could be successful in treating the disease or in raising the reduced level of the protein in the patient's liver. Accordingly, it is respectfully submitted that

the references are incompetent to set forth even a *prima facie* case of obviousness for the invention as claimed.

In view of the above, it is respectfully submitted that all rejections and objections of record have been successfully traversed and that the application is in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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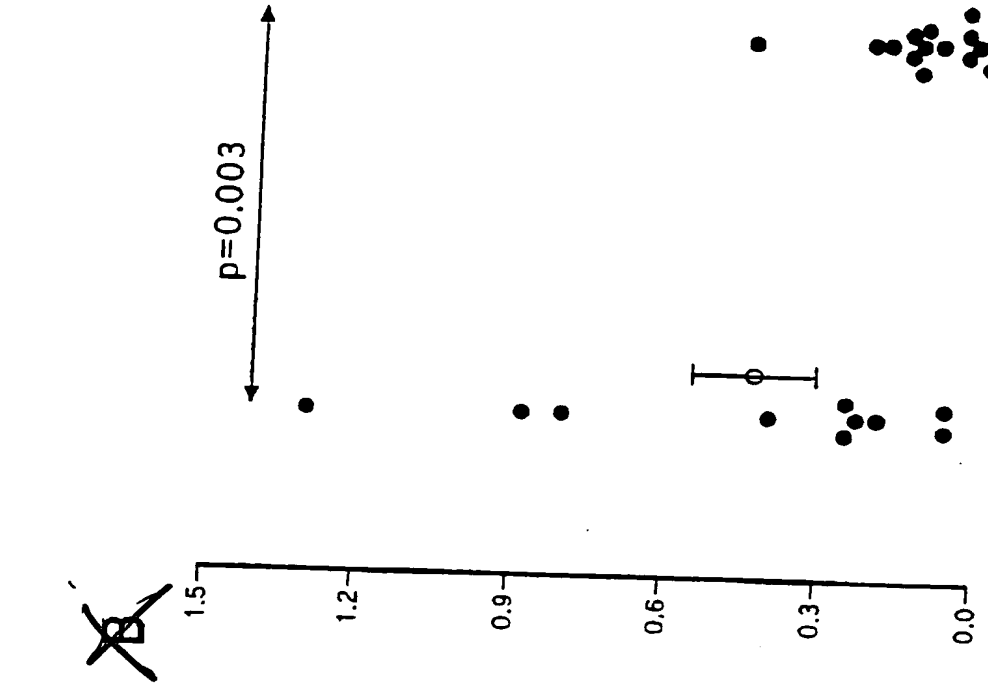

FIG. 1B

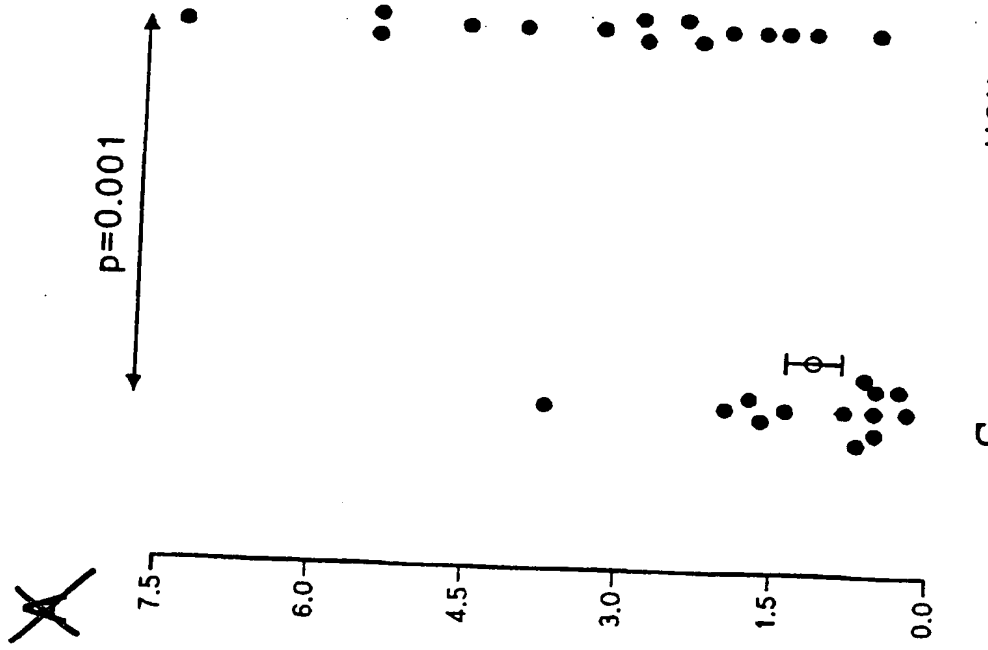

FIG. 1A

Figure 1

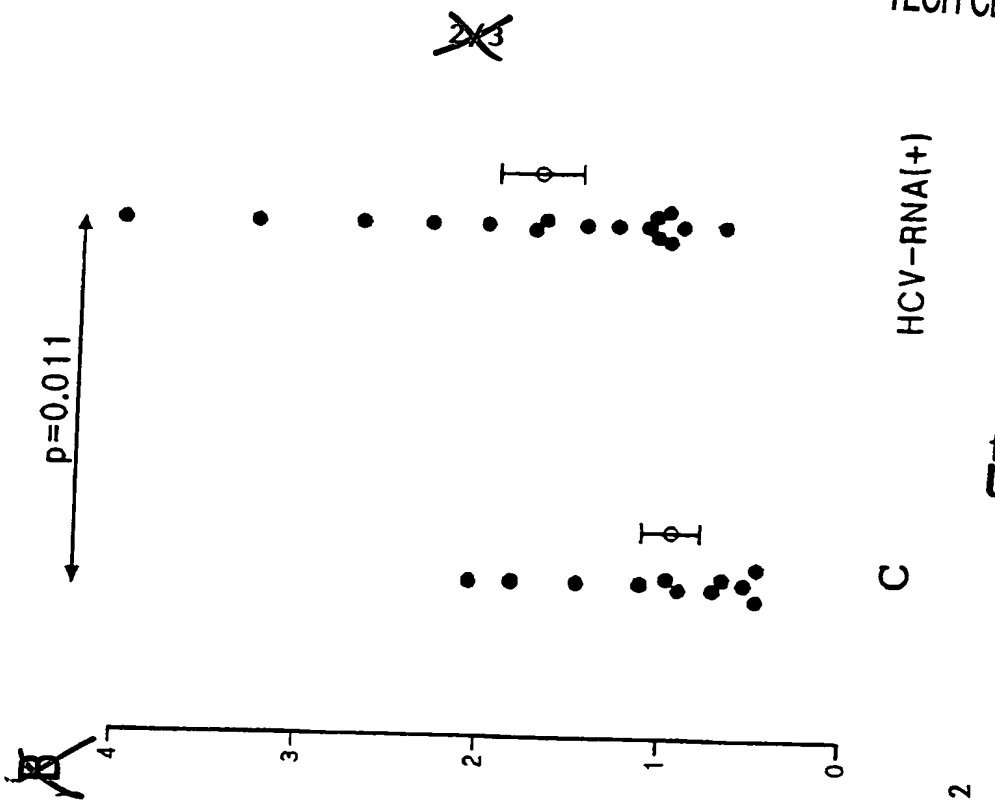

FIG. 2B

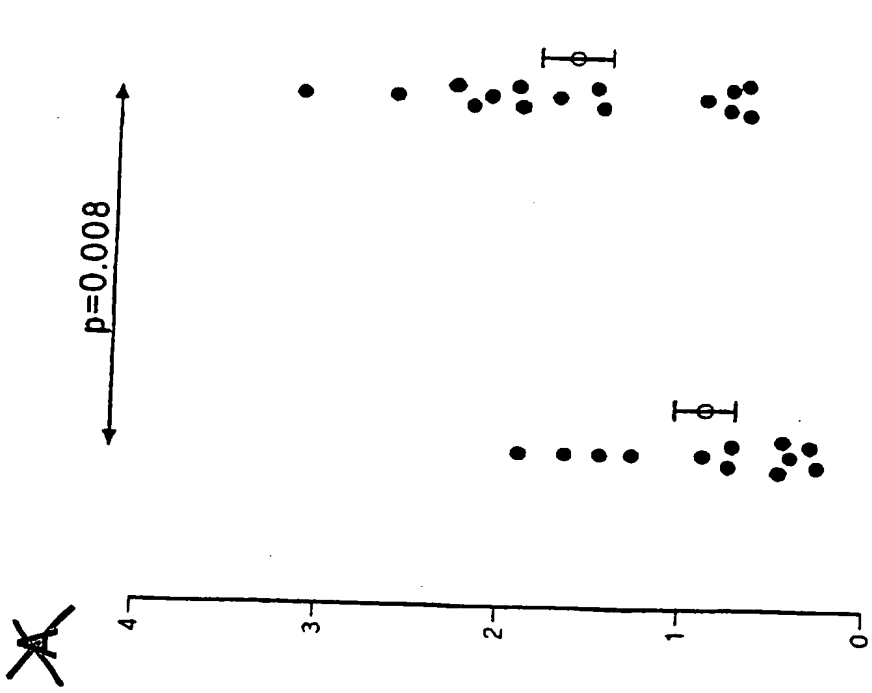

FIG. 2A

Figure 2

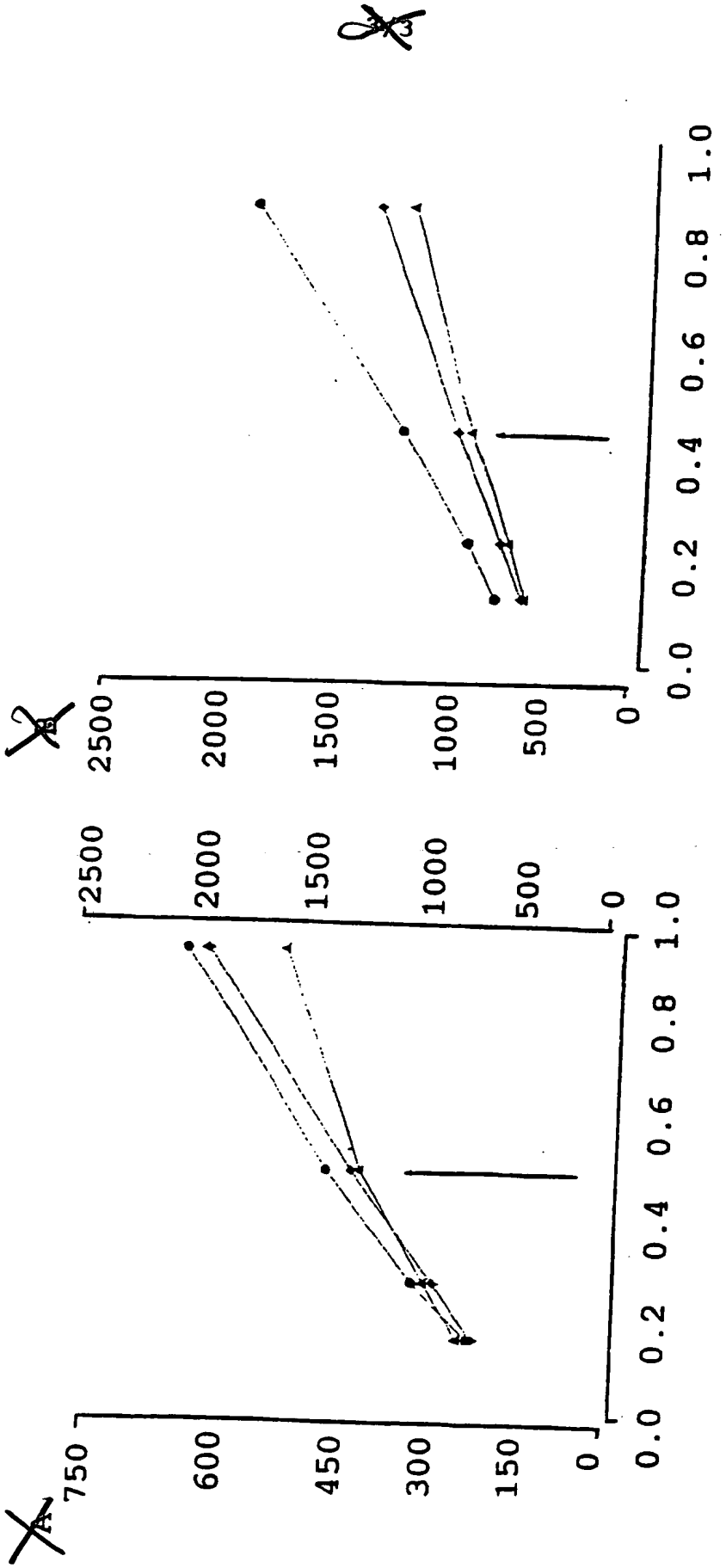

Figure 3

FIG. 3A

FIG. 3B